What is the invention?

Title: Hemodynamic Simulator

The invention is a device that experimentally simulates the real hemodynamic patterns of physiologic blood flow. Previous technology was limited to simulation of only the individual components of hemodynamic forces. The invention can simultaneously generate wall shear stress and circumferential strain patterns relevant to cardiovascular function and disease. The hemodynamic simulator can be used for clinical applications, medical research, and pharmaceutical delivery and development.

Invention Description

Problem Definition:

Cardiovascular disease is the leading cause of death in the US, costing millions of dollars per year. Atherosclerosis is the leading cause of death in the developed world and nearly the leading cause in the developing world. Associated systemic risk factors include hypertension, diabetes mellitus, hyperlipidemia, and smoking, among others. Research shows that atherosclerosis occurs in sites of complex hemodynamic behavior and consequently, motivates further investigation into the role hemodynamics in atherosclerosis. A major problem in coronary bypass surgery is the patency of the vessels to be used in the bypass. The bypass vessels are prone to failure after a short period of time, several years, and research points to the hemodynamic forces as the major contributor to the failure. Hemodynamic forces (forces due to blood flow) are known to influence blood vessel structure and pathology. The vascular cells lining all blood vessels, endothelial cells (ECs), are important sensors and transducers of the two major hemodynamic forces exposed to them: wall shear stress (WSS), the fluid frictional force per unit [surface] area, and hoop stress, driven by the circumferential strain (CS) of pressure changes. Wave reflections in the circulation and the inertial effects of blood flow cause a phase difference, stress phase angle (SPA), between CS and WSS. The SPA varies significantly throughout the circulation and is most negative in disease prone locations (i.e. the outer walls of a blood vessel bifurcation). Hemodynamic forces have been shown to dramatically alter endothelial function and phenotype (i.e. high shear stress [low SPA]- atheroprotective gene expression profile, and low shear stress [large SPA] - atherogenic gene expression profile). There is a great need to study vascular biology in a complete, integrative, and controlled natural hemodynamic environment.

Despite the significance of hemodynamic WSS and CS acting on the vessel wall, especially at regions of the circulation with a high risk of localization of cardiovascular diseases, detailed knowledge of the combined influence of the time varying patterns of WSS and CS on EC biological response remains technologically unfeasible.

What's new about the invention:

The hemodynamic simulator was designed to overcome current technological limitations in vascular research by physically simulating the normal and diseased physiologic states. A precise and complete physiologic environment is achieved via an

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uncoupling of the major hemodynamic forces, WSS and CS, which permits independent control over the magnitude and phase of the pulsatile WSS and CS to achieve a wide range of SPA. The robust invention experimentally simulates real hemodynamic patterns, complex and simple, while meeting the stringent requirements of sterility and minimal media volume demanded by cell and tissue culture systems.

The advantage of cell and tissue culture systems is that the tools of cell and molecular biology are easily employed. The integrative approach to the design of the hemodynamic simulator resulted in a system that is quick and easy to assemble and disassemble while maintaining cell culture integrity that is important for biological assays. The test chamber facilitates the insertion and removal of the test specimens. EC coated silicone elastic tubes are routinely placed in the hemodynamic simulator, yielding biological results relevant to the normal and diseased cardiovascular system.

The invention not only provides a means of studying hemodynamics in normal and diseased states, but it also can be used in tissue engineering, to test or train the function of bypass vessels prior to coronary bypass surgery, or to investigate cryopreserved vessels for research or medical use. Current coronary bypass surgery most often utilizes vessels from the hemodynamically unstrenuous saphenous vein (in the lower leg) as the bypass vessel. The invention can be used to train the vessel to the strenuous hemodynamic environment of the coronary arteries. All of these applications are ultimately related to the treatment of cardiovascular disease.

How the invention works:

The robust hemodynamic simulator neatly integrates engineering and biological principles by imposing a realistic, time varying mechanical environment on living vascular cells to provide a model of normal and diseased cardiovascular function that will help guide future therapeutic strategies, genetic or pharmacologic.

The new part of the invention is the uncoupling of pulsatile flow and pulsatile pressure to provide independent control over WSS and CS. The system at first seems paradoxical since it is classically well known that pressure and flow are coupled. However, in a dynamic sinusoidal environment, flow and pressure can be uncoupled.

The novel part of the apparatus is the drive system consisting of two reciprocating drive shafts that are coupled via a circular cam (cf. fig. 1, Flow Loop schematic). The flow shaft drives two piston pumps (at opposite ends) that are 180 degrees out-of-phase and are connected to the recirculating flow loop upstream and downstream of the test section. The flow shaft allows independent control of pulsatile flow with no pulsatile circumferential strain. The second (pressure) shaft also drives two piston pumps that are 180 degrees out-of-phase, however one piston drives the internal pressure upstream to the test section and the other piston drives the external chamber pressure. The pressure shaft allows for independent control of the pulsatile pressure. The attachment points of the circular cam that couples the two drive shafts can be adjusted to provide the phase(0-360deg) between the motions of the two shafts. This phase difference provides simulation of a wide range of SPA, including the diseased prone coronary arteries (-250 deg). Since the flow is related to wall shear stress (WSS) and the pressure is related to the circumferential strain (CS), we can say that the pulsatile WSS and pulsatile CS are independent and uncoupled.

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A videotape of a prototype hemodynamic simulator is provided to help illustrate the concept of uncoupling pulsatile pressure and pulsatile flow (cf. VHS Video - Hemodynamic Simulator). Further validation of the invention is provided in the form of synchronized and simultaneous data acquisition of flow, diameter, and pressure measurements. A data acquisition and analysis software was written in LabVIEW. An FFT analysis was performed to determine the phase difference between the sinusoidal waveforms (cf. figs 2-5- 0 deg, 60 deg, 90 deg, 180 deg). The pulsatile flow and WSS relationship was determined experimentally, numerically, and analytically previously in a vessel with same geometric and material properties [Qiu YC, 2000; Lee CS and Tarbell JM, 1997] .

Potential Benefits:

The cost of constructing, operating, and maintaining the hemodynamic simulator were major design criteria. The design may be difficult to grasp conceptually, however the system is robust and simple, hence, requiring few parts except for the main drive system. The tube lengths and diameters, tube fittings, media volume, cell number, and test section dimensions were all minimized to provide the ideal cell and tissue culture environment. Auroclavable tubing and other parts promote reuse and recycling. The hemodynamic simulator is a low cost model capable of generating the complete range of hemodynamic force patterns for cardiovascular researchers and will open new avenues of research and development never before possible at any cost. The device will soon be a standard optional tool for cardiovascular researchers and will greatly accelerate our current understanding of cardiovascular function and disease. New pharmacologic and genetic strategies can be tested with the system at much lower costs than conventional methods of animal experimentation. Ultimately, patients will benefit the most since the hemodynamic simulator will advance new concepts in cardiovascular disease progression, development. and treatment. Healthy patients can function as productive members of society, improve their quality of living, and reduce the cost of medical treatment.

Improvement upon prior technology:

Prior technology focused on the individual effects of WSS or strain on ECs separately applied. The most common WSS simulating systems utilize a 2-dimensional stiff surface for the EC culture forming the wall of a parallel plate flow chamber. In these devices, the WSS is usually steady due to difficulties in simulating pulsatile flow. The cyclic straining devices provide only strain by stretching cells on a compliant membrane without flow. Both types of systems are obviously limited by their design. A silicone tube coated with ECs was introduced in the mid-90's and provided, for the first time, the potential for simultaneous coupled pulsatile strain and shear stress. However, these tubes were used in flow simulators coupling pressure and flow that could only achieve phase angles (SPA) of about 90 degrees. This is inadequate for simulating coronary arteries (SPA = 250 degrees), the most disease prone vessels in the circulation. The hemodynamic simulator provides the most complete physiologic environment by providing time-varying uniform cyclic CS and pulsatile WSS in a 3-dimensionsal configuration over a complete range of SPA.

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Roles of inventors:

The advisor, John Tarbell, identified and clarified the problems of investigating the complete hemodynamic forces involved in normal and diseased vascular biology. The design requirements and constraints, such as correct physiologic simulation, sterility, and minimal media volume, were provided by Dr Tarbell, as well as the validation of the relation of pulsatile flow and WSS. The student, Michael Dancu, designed, developed, constructed, tested, and validated the system as well as a data acquisition system and software.

Appendix

A list of research papers utilizing prior technologies is presented here. The device that simulates steady wall shear stress is a rod and plate system (Berthiaume and Frangos, 1995), similar to a cone and plate system used in viscometers. Parallel flow chambers simulate steady flow as well (Chang YS, 1998). The device to simulate cyclic strain consists of a flexible membrane that is stretched via a motor or vacuum suction system (Carosi et al, 1992; Sumpio et al., 1990). A device to simulate pressure and flow in tubes was done by Qiu and Tarbell, 2000. This device did not permit a wide range of phase angles (SPAs) and was difficult to use. An in vitro study verifies that simulation of the hemodynamic environment is critical to vessel patentcy and function (Seliktar et al., 2000).

Patent and literature searches for all the keywords pertaining to the invention yields proof of no existing devices.

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